

REMARKS

Claims 27-36 have been added. Support for the new claims can be found in original Claims 1-9 and 26, on page 27, lines 26-27, and on page 28, lines 2-5, for example. The new claims add no new matter.

Information Disclosure Statement

An Information Disclosure Statement (IDS) is being filed concurrently herewith. Entry of the IDS is respectfully requested.

CONCLUSION

The Examiner is respectfully requested to enter the amendments. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (978) 341-0036.

Respectfully submitted,

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MARKED UP VERSION OF AMENDMENTSSpecification Amendments Under 37 C.F.R. § 1.121(b)(1)(iii)

Replace the paragraph at page 25, lines 6 through 19 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

Biologically active NO can be measured as S-nitrosothiol (in the form of SNO-Hb) and iron nitrosylhemoglobin. Red blood cells of normal humans have been found to carry a range of biologically active NO. See Figures 12A, 12B and 12C. According to these measurements on red blood cells of freshly drawn human blood, the mean value for total NO:Hb as a molar ratio, for NO in the form of S-nitrosothiol and iron nitrosylhemoglobin, is approximately 0.0030. The range of NO:Hb values measured in normal humans was approximately 0.0002 to 0.0060. Desirable ranges of NO:Hb in blood can be, for example, approximately 0.0002 to 0.0010, 0.0010 to 0.0020, 0.0020 to 0.0030, 0.0030 to 0.0040, 0.0040 to 0.0050, and 0.0050 to 0.0060. Desirable values for NO:Hb in blood can be, for example, approximately 0.0010, 0.0020, 0.0030, 0.0040, 0.0050, or 0.0060, [and the mean of] the mean being approximately 0.0030. A desirable ratio of SNO to total NO is approximately 0.5, as measured in arterial blood. In some cases, it may be desirable or necessary to increase NO:Hb to as much as about 0.04, to bring about a pharmacological or therapeutic effect.

Replace the paragraph at page 28, line 18 through page 29, line 2 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

A further method to raise NO:Hb is the administration to the human of NO as an inhaled gas or the administration to the human of NO dissolved in a physiologically compatible carrier (a buffer or saline, for example) to be delivered by a parenteral method. A liquid solution of NO can be prepared by dissolving it at 0.1 to 1.9 mM in anaerobic saline. The solution can then be infused at

0.1-100 nmoles/kg. By increasing NO:Hb, preferably restoring the NO:Hb to a value within the normal range, the level of SNO-Hb within the red blood cells is increased. This allows for the facilitation of transnitrosation reactions by which biologically active NO is transferred out of the red blood cell to exert the physiological effects that have been attributed to nitric oxide or EDRF. See, for example, Pawloski, J.R. *et al.*, *Nature* 409:16738-16745 (2001); Hess, D.T. *et al.*, *Nature Cell Biol.* [3:E46-#49] 3:E46-E49 (2001); and Mato, J.M. *et al.*, *Nature Medicine* 7(10):1107-1108 (2001).